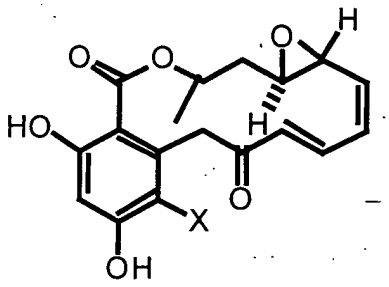
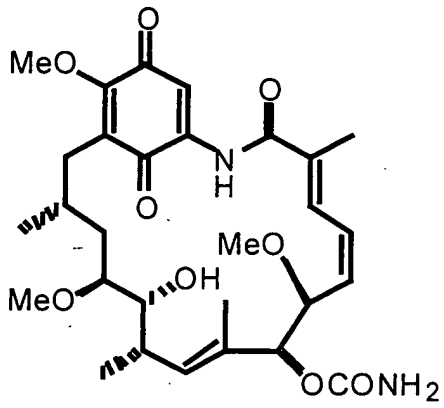
Figure 1. Structures of Monocillin I, Radicicol and Geldanamycin



X = Cl Radicicol (**1**)
X = H Monocillin I (**2**)



Geldanamycin (**3**)

Figure 1

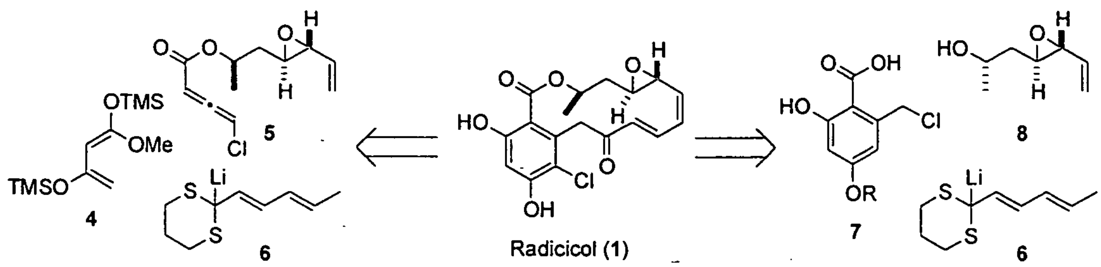
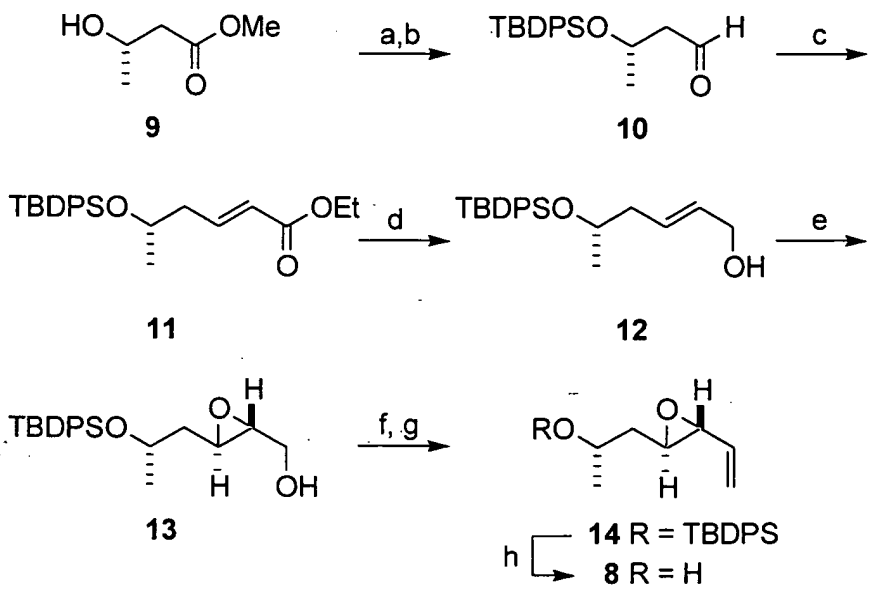

OTMS
OMe
TMSO
4
5
Cl
Li
S
S
6
HO
Cl
OH
Radicicol (1)
OH
HO
Cl
OR
7
HO
8
Li
S
S
6

Figure 2



(a) TBDPSCl, imid., >95%; (b) DIBAL-H, –78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL-H, –20 °C, 96%; (e) (+)-DET, $Ti(OiPr_4)$, TBHP, 90%, >95% ee; (f) SO_3•pyridine, Et_3N, DMSO, 90%; (g) Ph_3PCH_3Br, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.

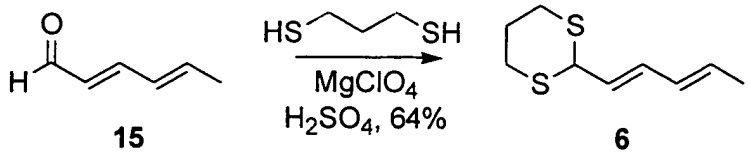
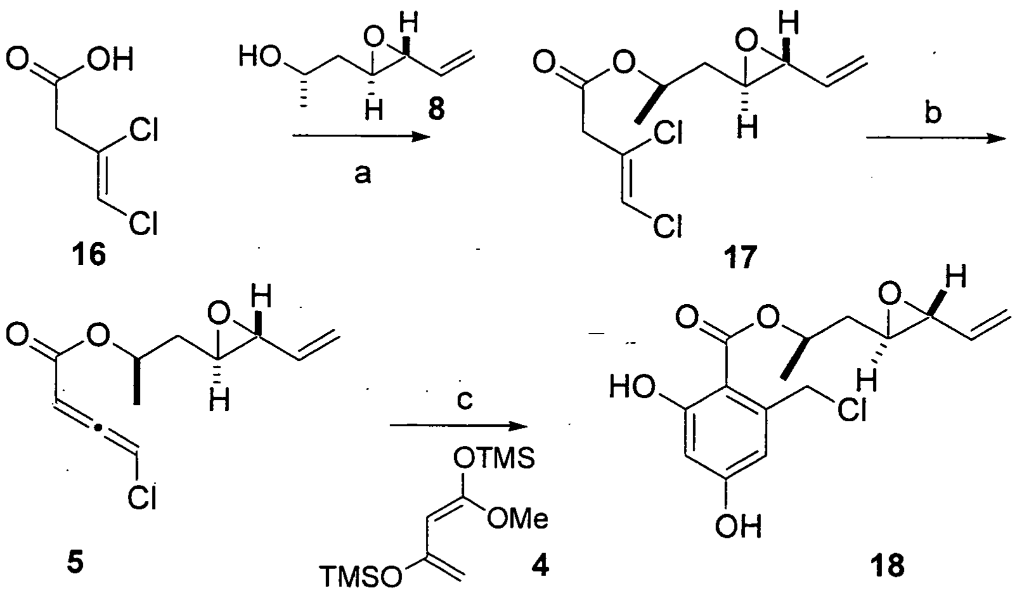


Figure 3



a. DEAD, PPh_3, 70%; b. iPr_2NEt, 70%; c. 50% (4:1)

Figure 4

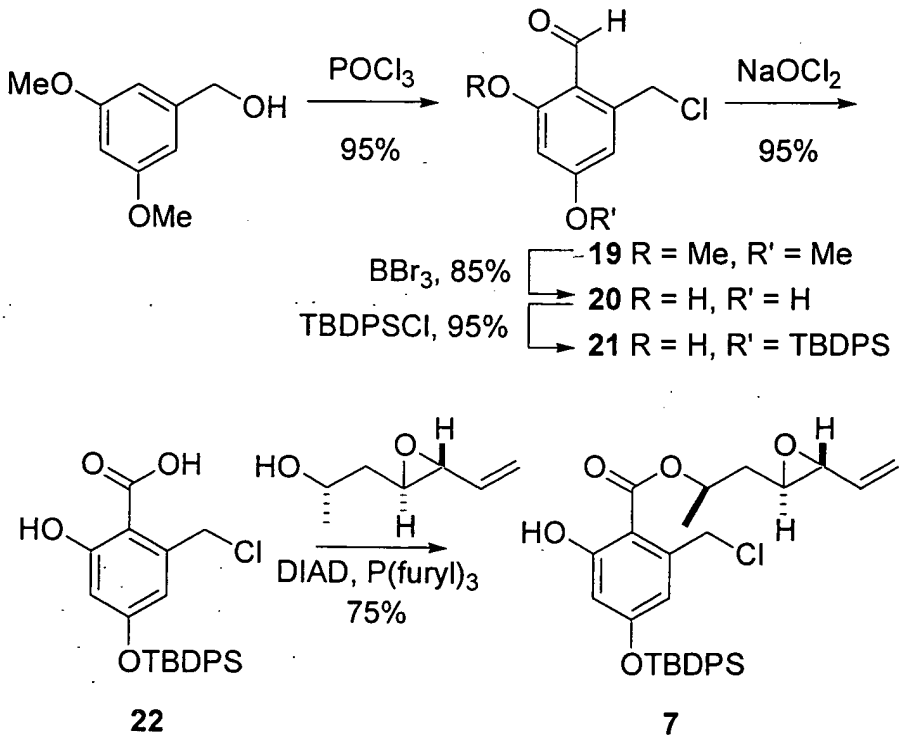
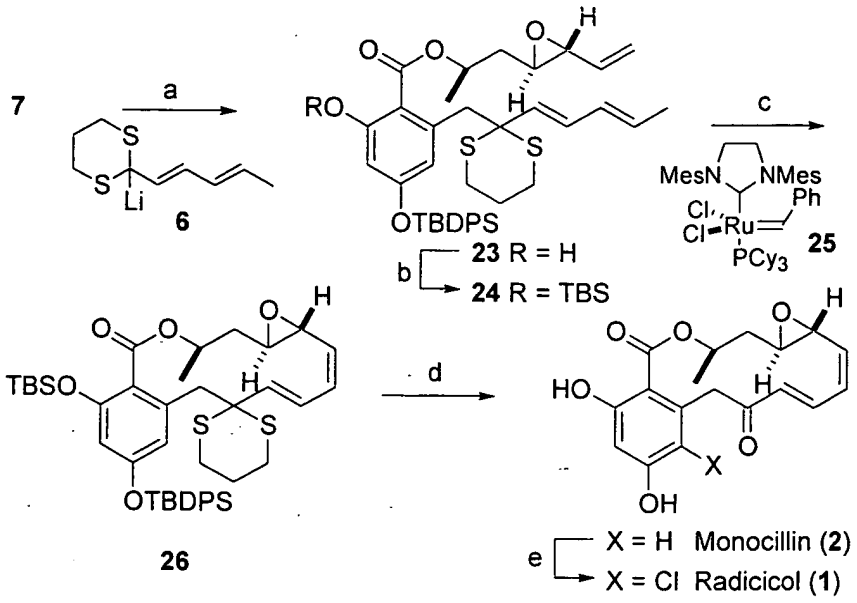


Figure 5



a. *n*-BuLi, –78° C, 50% (6:1); b. TBSCl, 83%; c. 42 °C, 70%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60°C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 50%

Figure 6

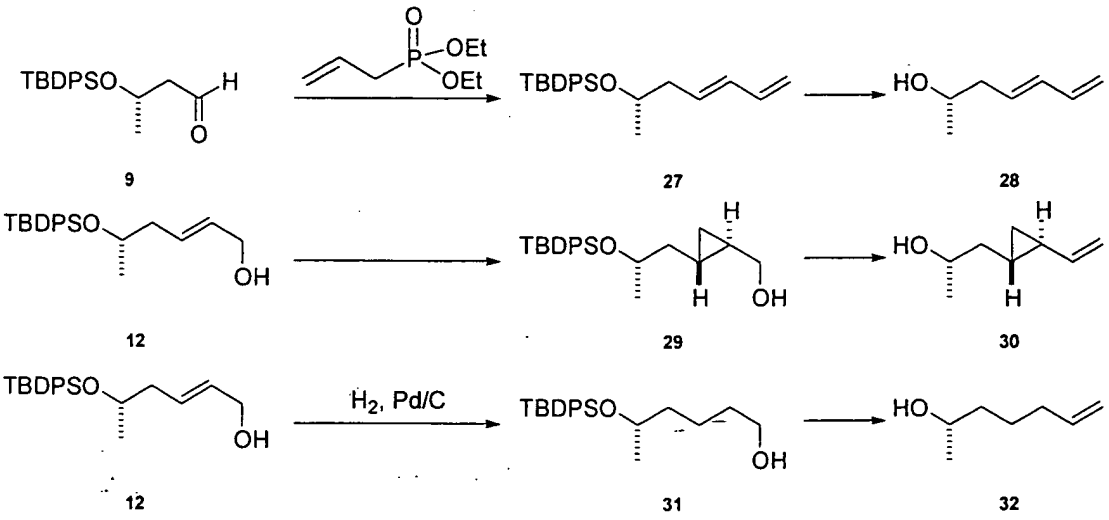
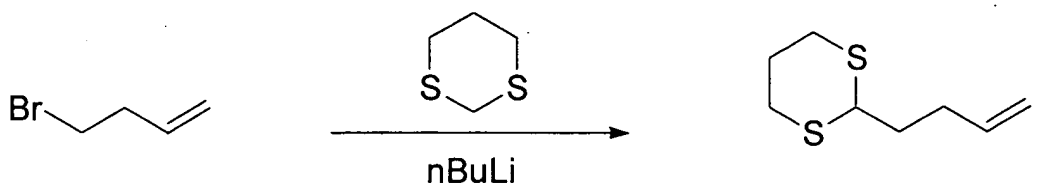

TBDPSO
H
O
O
P
OEt
OEt
TBDPSO
HO
9
27
28
TBDPSO
OH
TBDPSO
H
H
OH
HO
H
H
12
29
30
TBDPSO
OH
H2, Pd/C
TBDPSO
OH
HO
12
31
32

Figure 7



33 34

Figure 8

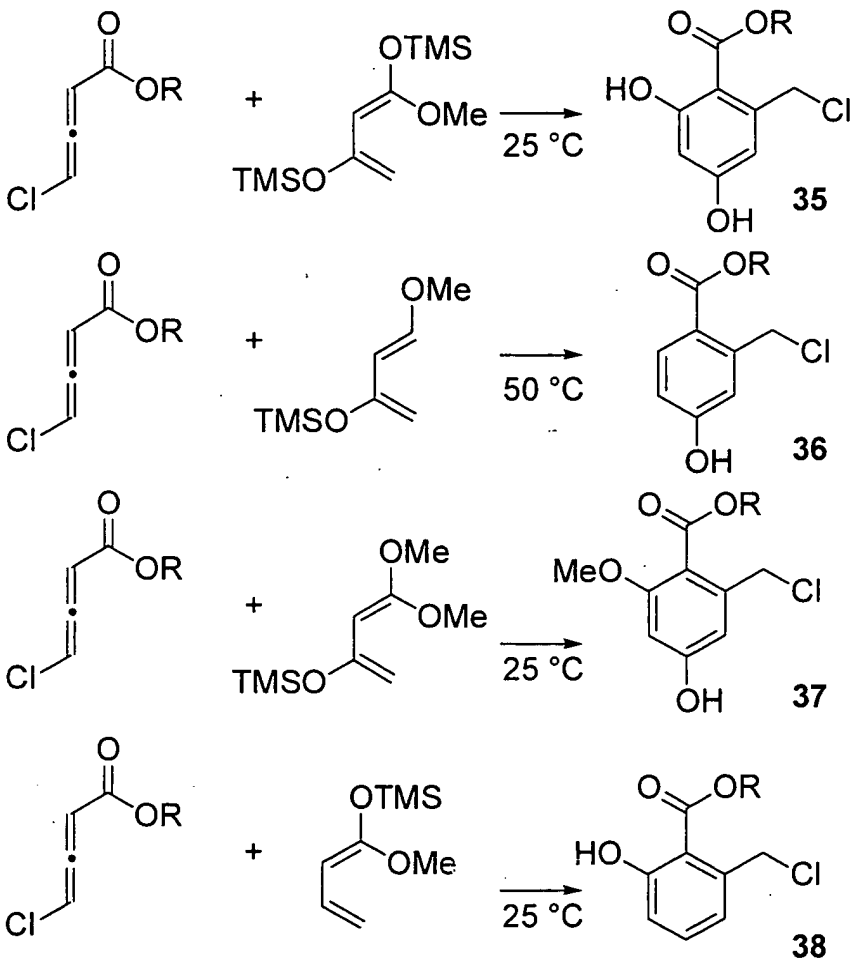
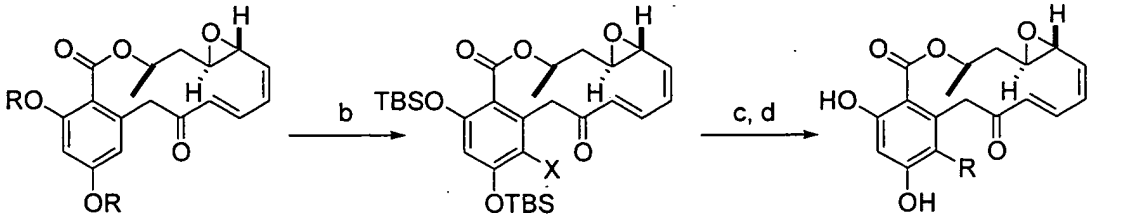


Figure 9

Generation of Diversity at Aromatic Positions



a. TBSCl, pyridine; b. NIS or NBS, TsOH; c. $Pd(PPh)_3$, $RSnBu_3$; d. nBu_4NF

Figure 10

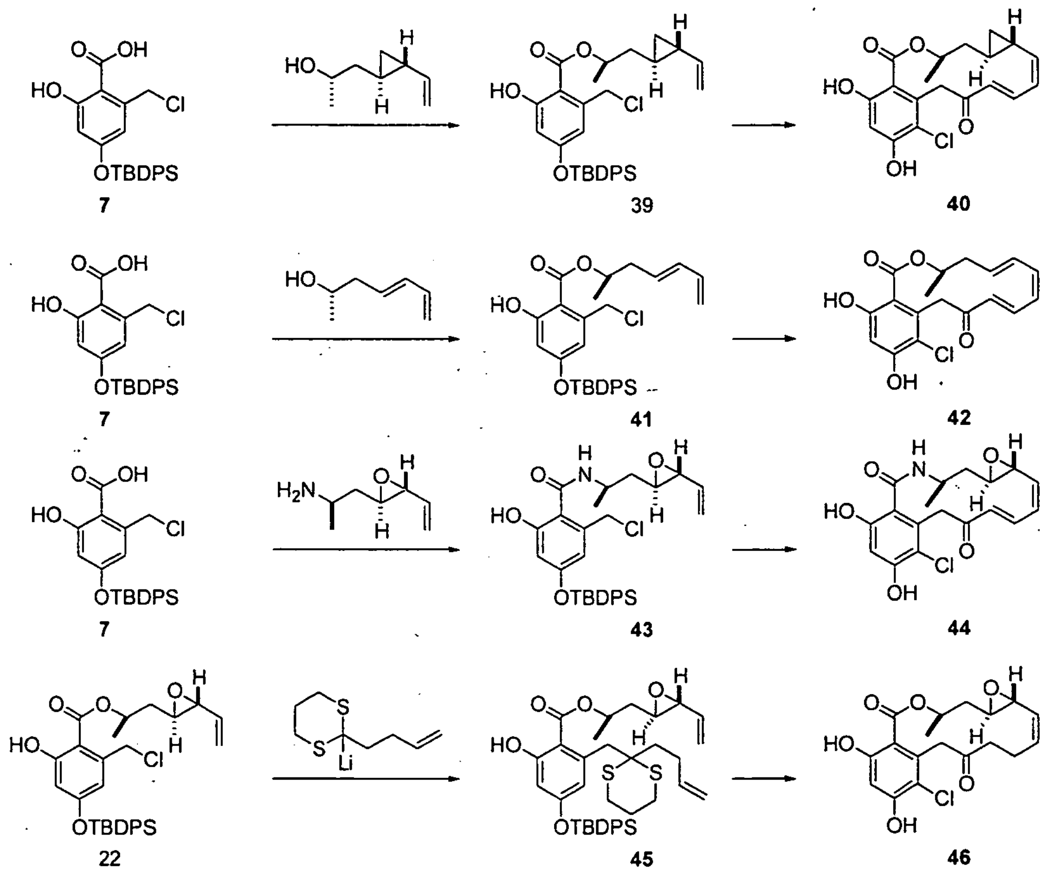


Figure 11

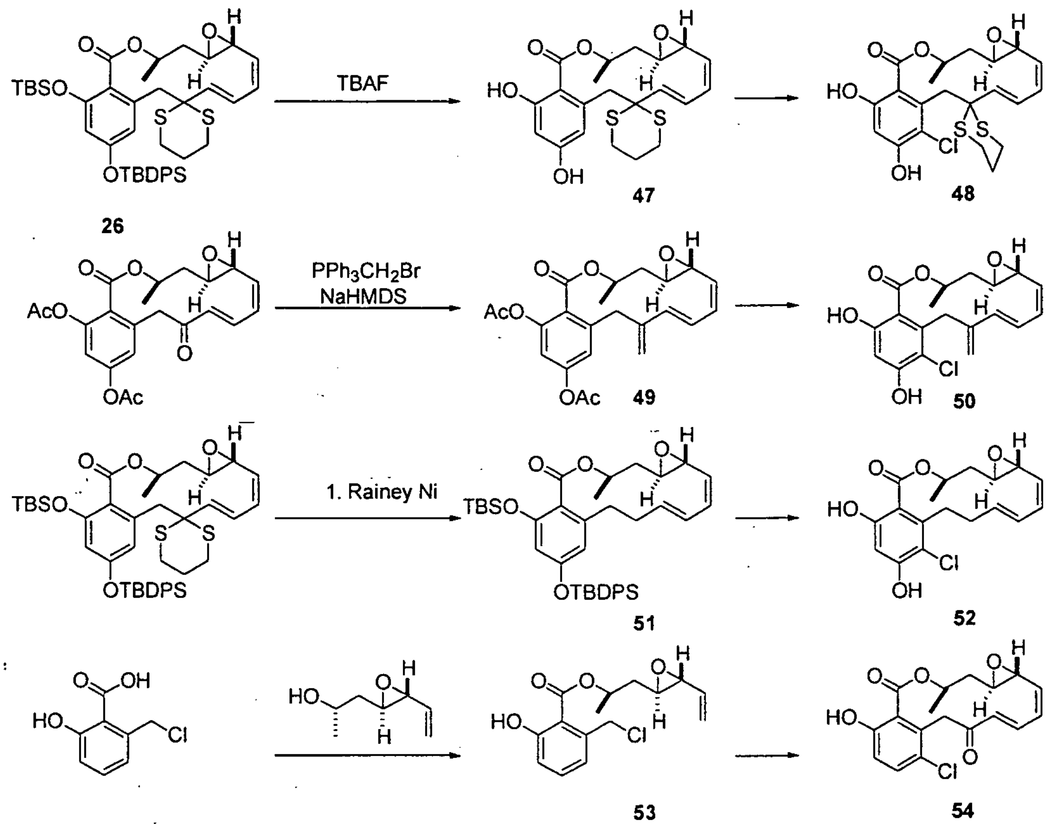
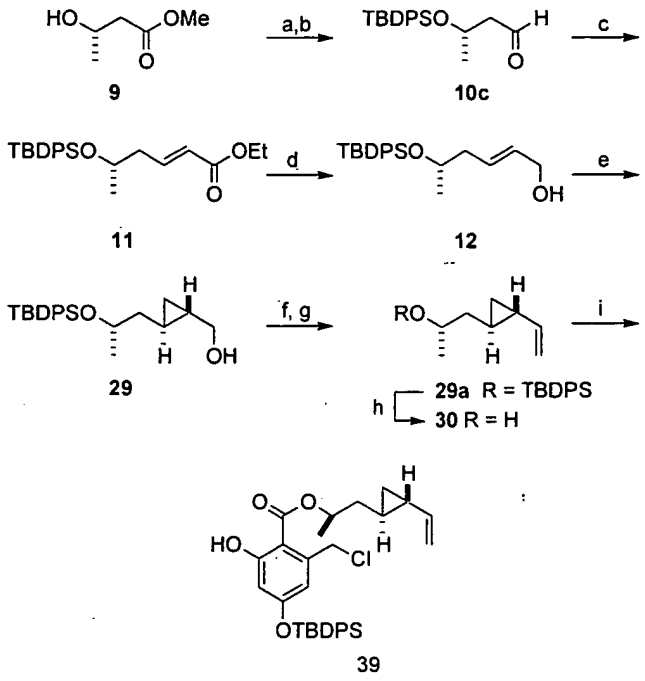
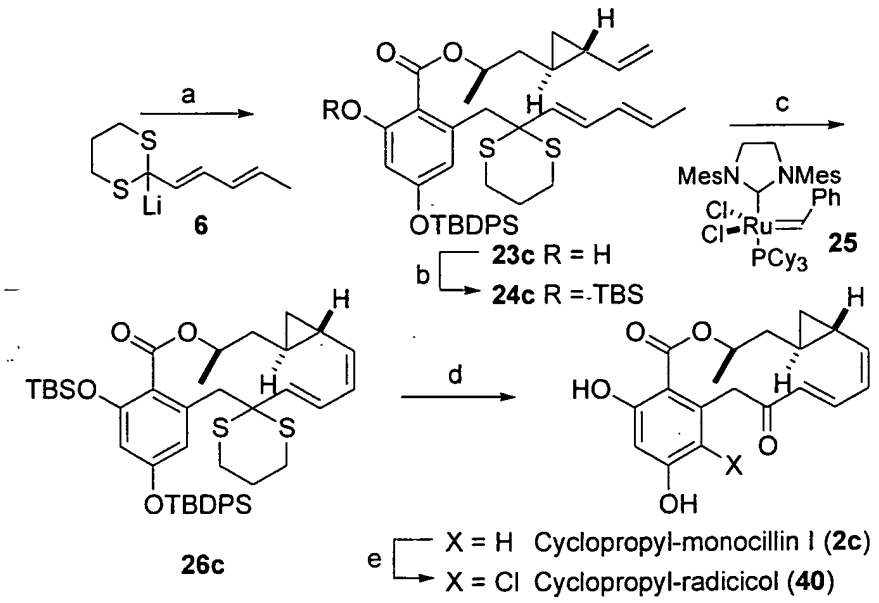

TBSO
OTBDPS
26
TBAF
HO
OH
47
48
Cl
AcO
OAc
PPh3CH2Br
NaHMDS
49
50
1. Rainey Ni
TBSO
OTBDPS
51
52
OH
HO
Cl
53
54

Figure 12



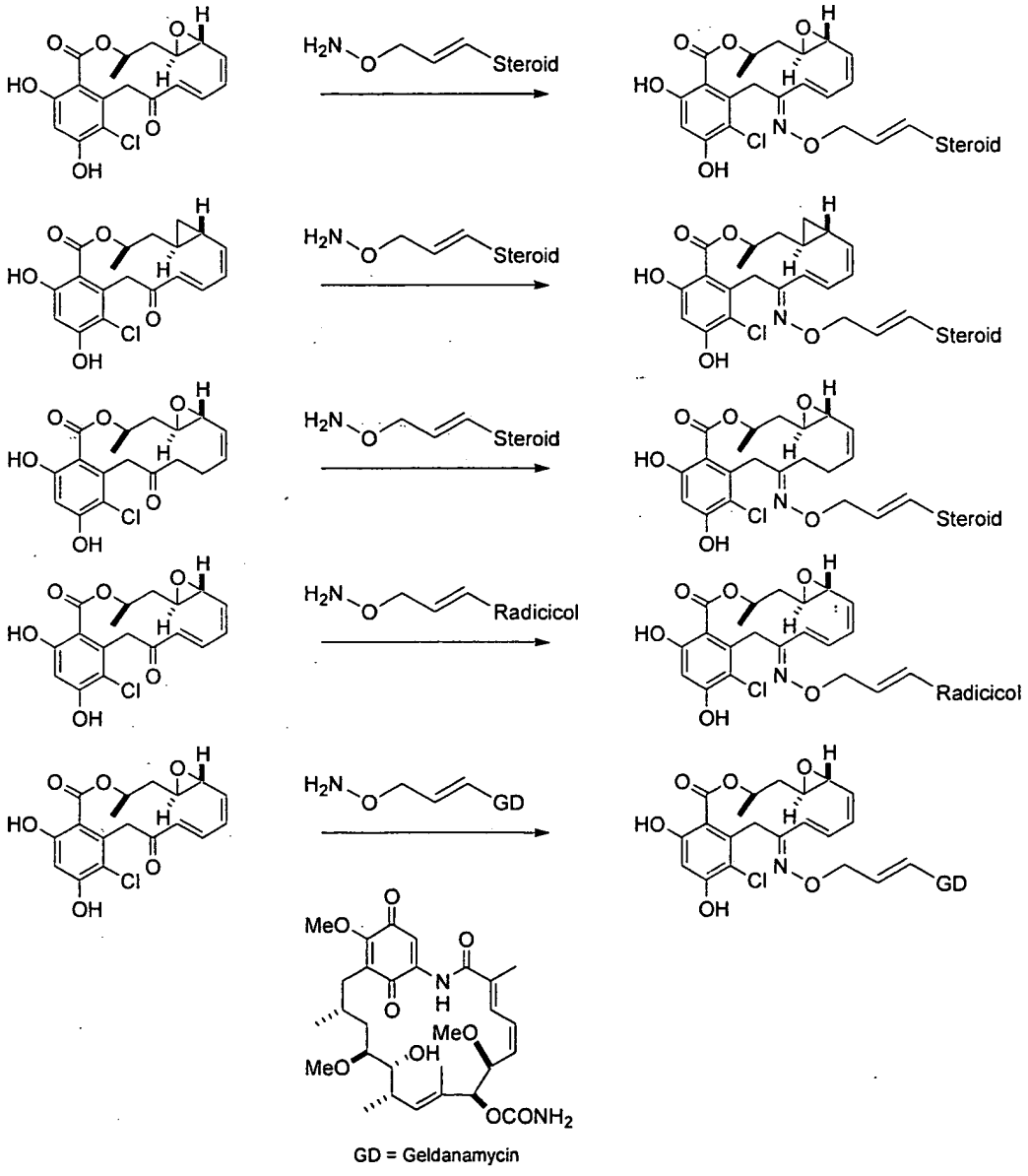
[a] (a) TBDPSCl, imid., >95%; (b) DIBAL-H, –78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL-H, –20 °C, 96%; (e) (+)-tetramethyltartaricacid diamide-BBu, Et_2Zn, CH_2I_2, 9 >95% ee; (f) SO_3•pyridine, Et_3N, DMSO, 90%; (g) Ph_3PCH NaHMDS, 0 °C, 82%; (h) TBAF, 89%; (i) 7 , P(furyl)$_3$, DIA benzene, 60%

Figure 13



a. *n*-BuLi, –78° C, 75% (3:1); b. TBSCl, 83%; c. 42 °C, 20%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60°C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 80%

Figure 14



GD = Geldanamycin

Figure 15

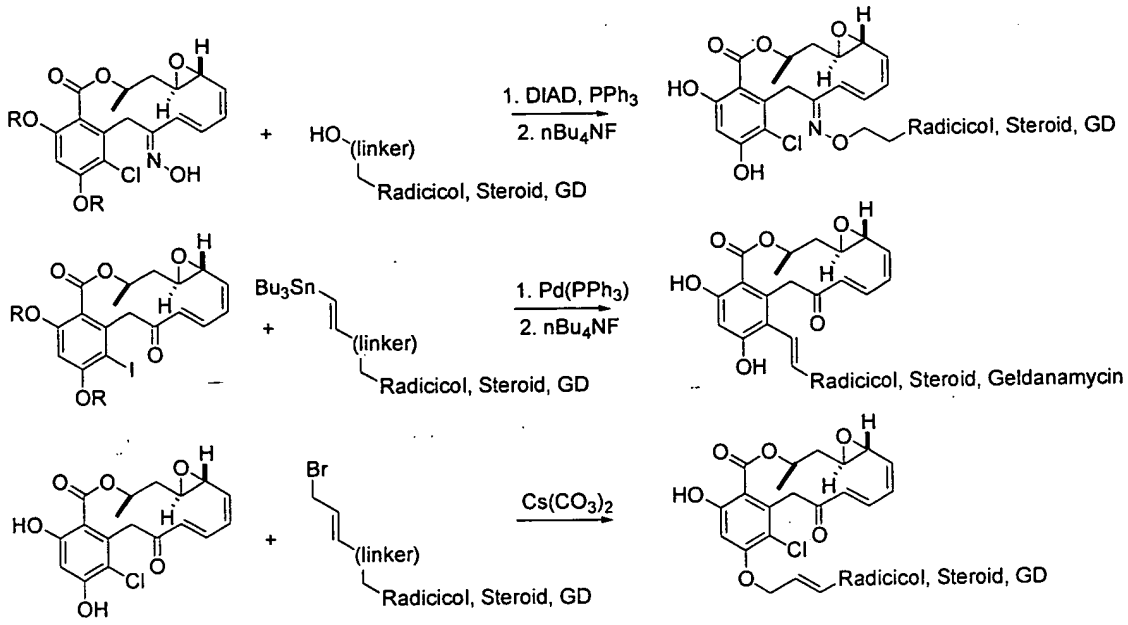
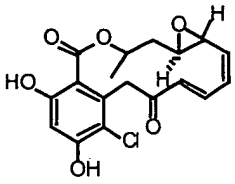
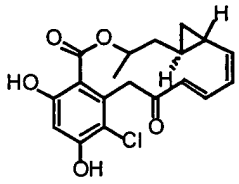

1. DIAD, PPh3
2. nBu4NF
HO (linker) Radicicol, Steroid, GD
Radicicol, Steroid, GD
Bu3Sn (linker) Radicicol, Steroid, GD
1. Pd(PPh3)
2. nBu4NF
Radicicol, Steroid, Geldanamycin
Br (linker) Radicicol, Steroid, GD
Cs(CO3)2
Radicicol, Steroid, GD

Figure 16

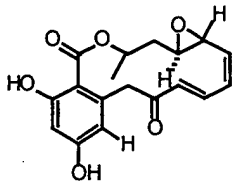
I. Radicicol



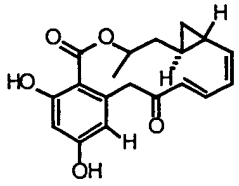
III. Cyclopropyl radicicol



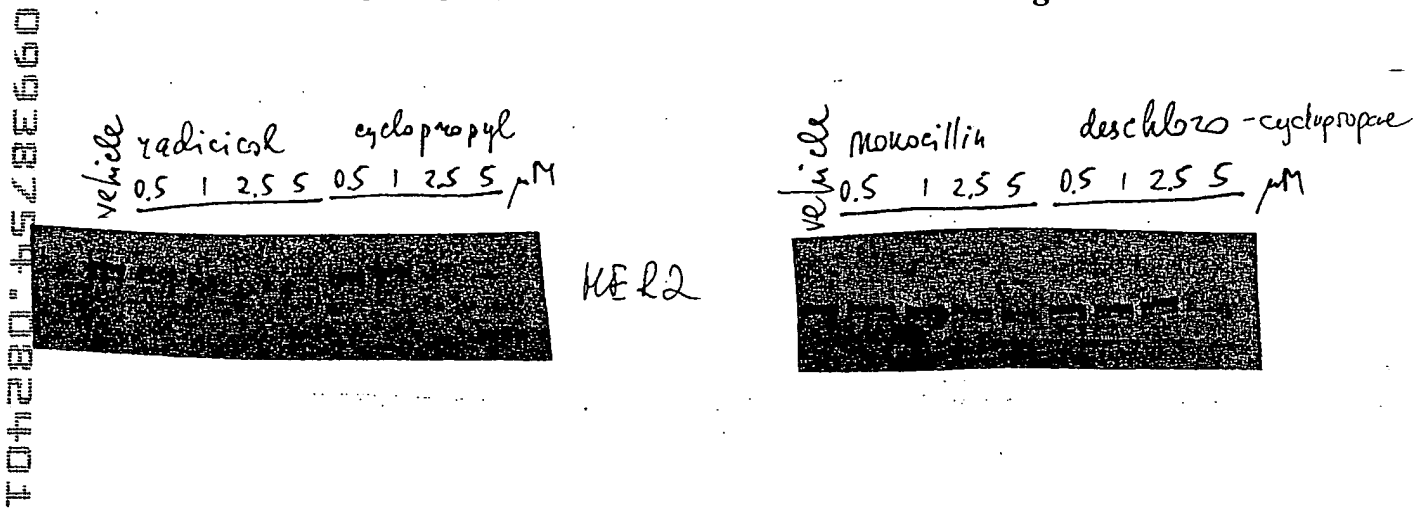
II. Monocillin I



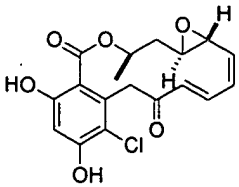
IV: Cyclopropyl monocillin



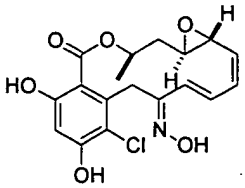
MCF7 Cells Treated with Radicicol and Analogues



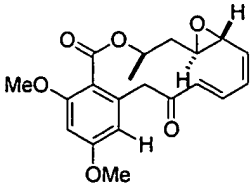
I. Radicicol



VII. Radicicol Oxime



V. Dimethyl Monocillin I



VI. Dimethyl Radicicol

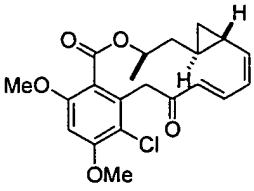
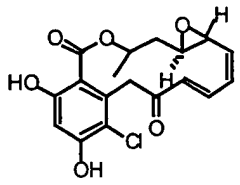
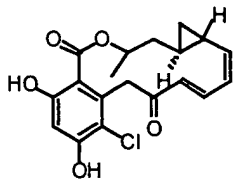


Figure 17

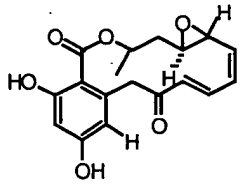
I. Radicicol



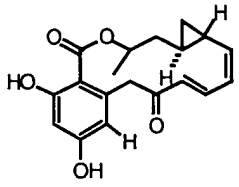
III. Cyclopropyl radicicol



II. Monocillin I



IV: Cyclopropyl monocillin



BT474 Cells Treated with Novel Radicicols (24 hrs.)

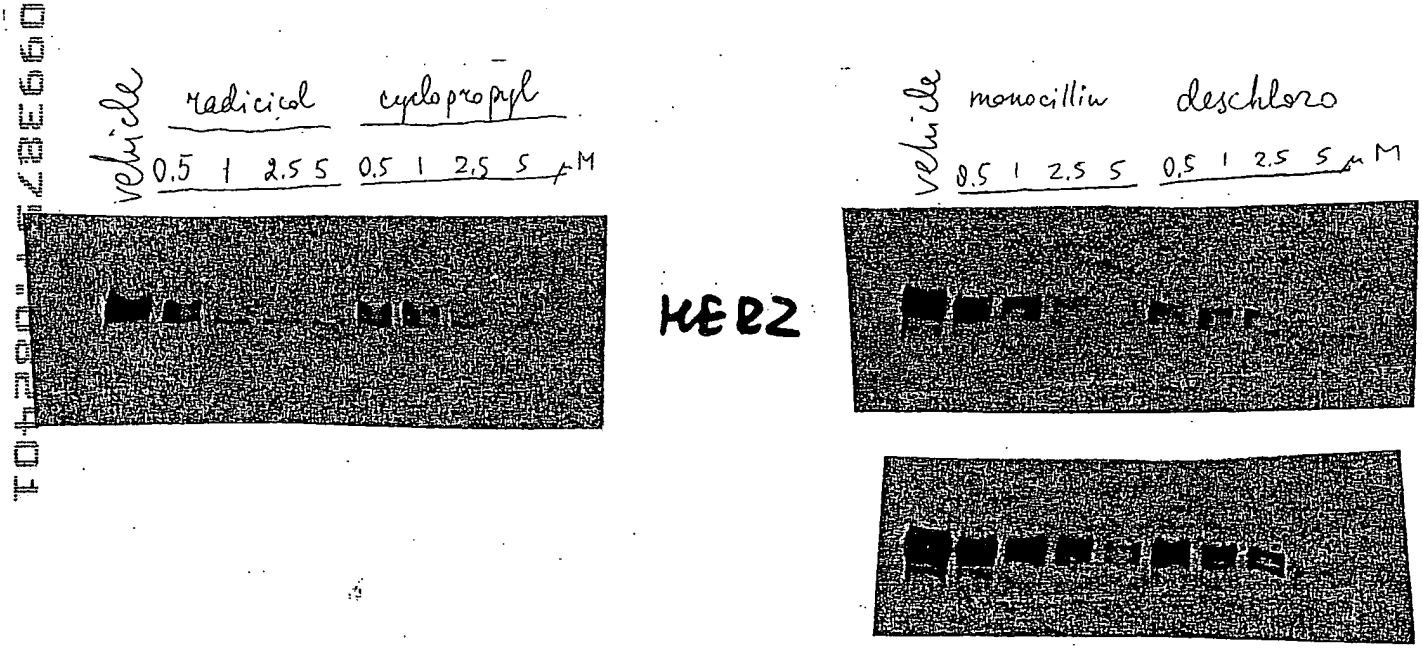


Figure 18

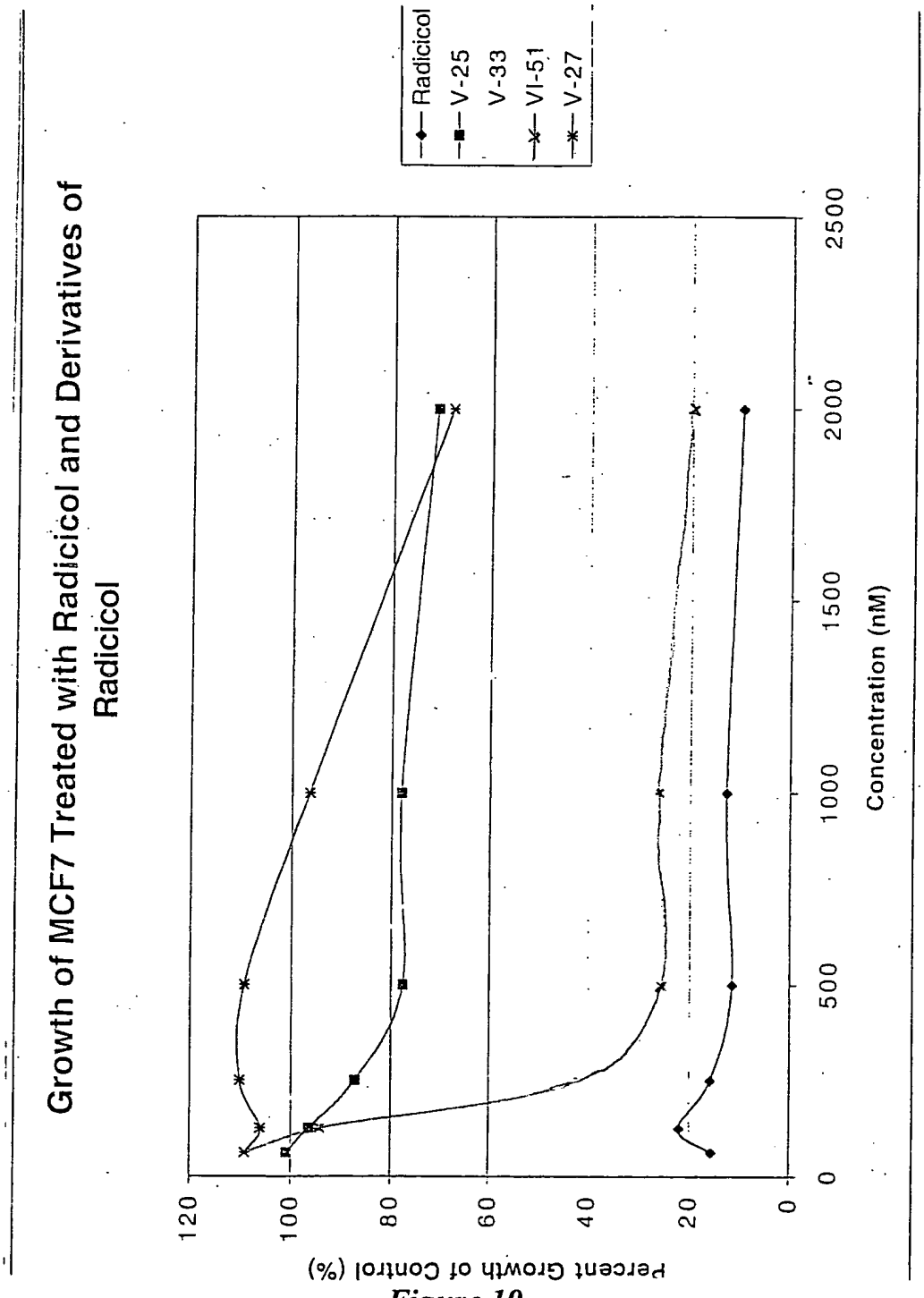

Growth of MCF7 Treated with Radicicol and Derivatives of Radicicol
Radicicol
V-25
V-33
VI-51
V-27
Percent Growth of Control (%)
120
100
80
60
40
20
0
0
500
1000
1500
2000
2500
Concentration (nM)

Figure 19

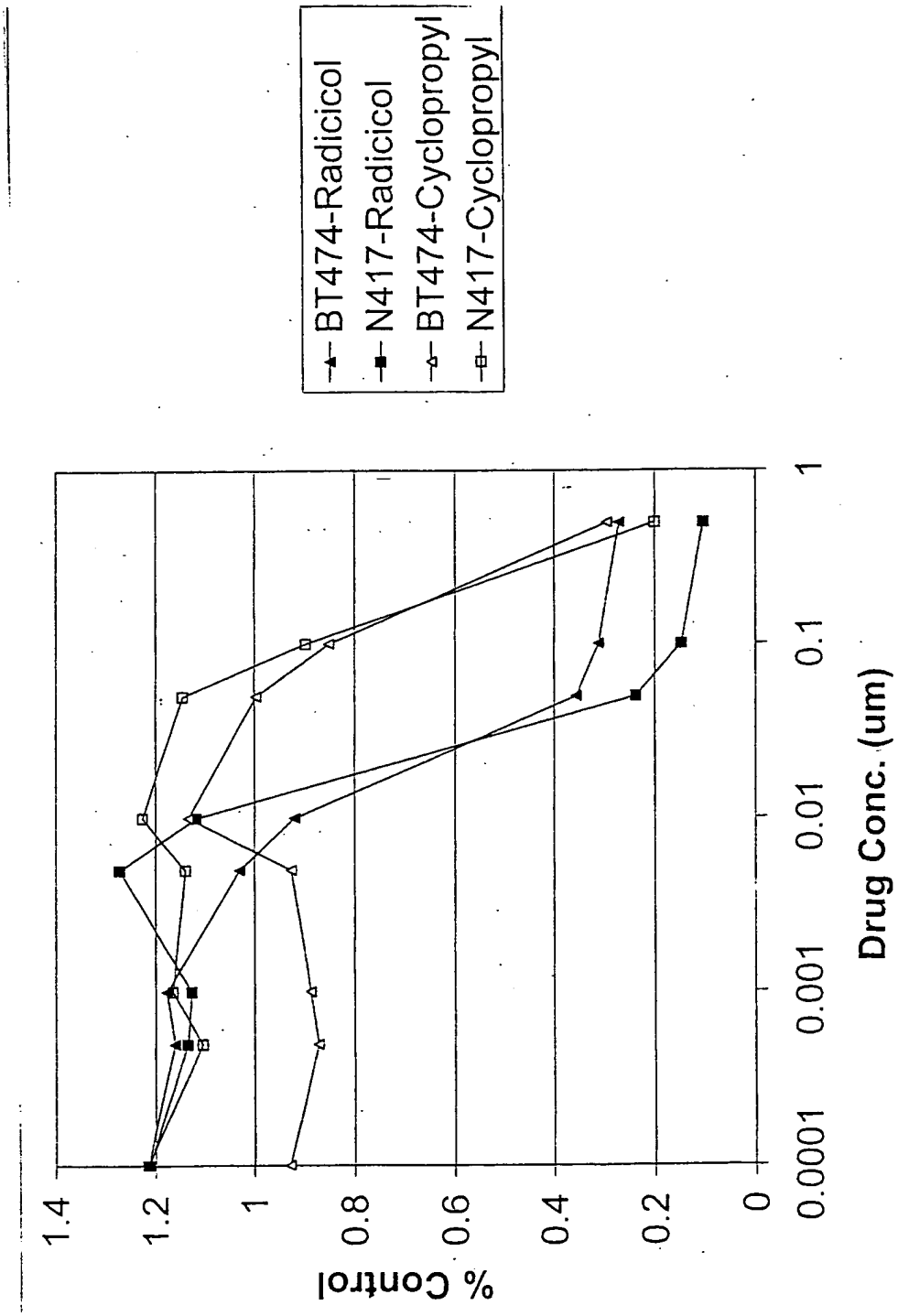

BT474-Radicicol
N417-Radicicol
BT474-Cyclopropyl
N417-Cyclopropyl
% Control
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.0001
0.001
0.01
0.1
1
Drug Conc. (um)

Figure 20

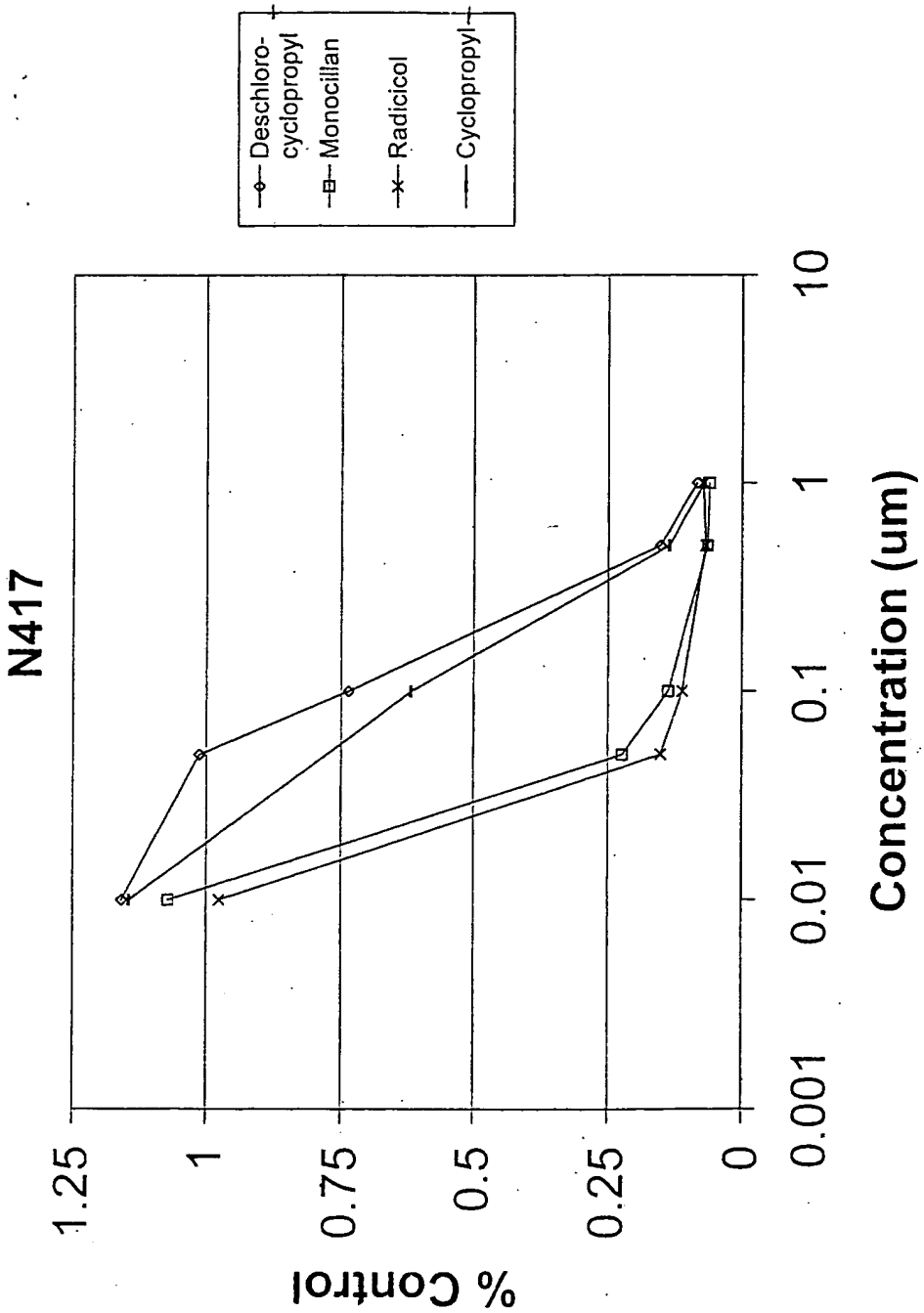

Deschloro-cyclopropyl
Monocillan
Radicicol
Cyclopropyl
N417
% Control
1.25
1
0.75
0.5
0.25
0
0.001
0.01
0.1
1
10
Concentration (um)

Figure 21